REVIEW

Therapeutic hypothermia following perinatal asphyxia

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Well constructed and carefully analysed trials of hypothermic neural rescue therapy for infants with neonatal encephalopathy have recently been reported. The data suggest that either selective head cooling or total body cooling reduces the combined chance of death or disability after birth asphyxia. However, as there are still unanswered questions about these treatments, many may still feel that further data are needed before health care policy can be changed to make cooling the standard of care for all babies with suspected birth asphyxia.

Extensive experimental data suggesting that a reduction in body temperature of about 3°C following cerebral hypoxia-ischaemia reduces cerebral injury and improves functional outcome has prompted clinical evaluation of hypothermic neuroprotective therapy. Preliminary studies in neonates suffering from perinatal asphyxia demonstrated the feasibility of therapeutic hypothermia and full randomised trials are in progress or have been completed. How strong is the current evidence supporting therapeutic mild hypothermia and should this intervention become standard care for asphyxiated newborns?

EVIDENCE FROM EXPERIMENTAL STUDIES

Studies of mild hypothermia for neural rescue after perinatal asphyxia began when experimental studies in animals suggested that mild hypothermia applied soon after hypoxia-ischaemia lessened pathophysiological abnormalities and improved functional outcome.¹ Several studies confirmed that post-insult cooling reduced injury in immature animals.^{2–5}

The mechanism of protection is still unclear. However, hypothermia ameliorates the pathophysiological processes that follow cerebral insults: mild hypothermia attenuates blood-brain barrier damage, release of excitatory neurotransmitters is reduced, free radical production is lessened, and IL-10 (an anti-inflammatory cytokine) is increased.^{6–12} Cooling has positive effects on cerebral metabolism both during and following cerebral insults. Hypothermia decreases the cerebral metabolic rate for glucose and oxygen, reduces the loss of high energy phosphates during ischaemia, and prevents or ameliorates secondary cerebral energy failure.^{4 13} Importantly, hypothermia influences apoptotic mechanisms within cells: caspase 3 activity is lessened and cytochrome *c* translocation is diminished, resulting in a reduction in apoptotic neurons.^{14–16}

Review of experimental studies of focal cerebral ischaemia indicates that mild hypothermia is associated with an approximately 50% reduction in infarct size. Following global hypoxic or hypoxic-ischaemic or traumatic insults, mild hypothermia reduces damage in the cortex, thalamus, and hippocampus. Treated animals also demonstrate preserved neurological functions. Although some of these benefits may diminish over time, the protection provided by post-insult hypothermia generally persists.^{17 18}

CLINICAL STUDIES IN ADULTS

In the 1990s, promising results were reported in preliminary clinical studies of mild hypothermia following traumatic brain injury. However, in a recent meta-analysis and systematic reviews of all clinical studies of neuroprotection with mild hypothermia following traumatic brain injury, there was no evidence of benefit with hypothermia and there was increased sepsis in cooled patients.^{19–21} Possible explanations of the failure to demonstrate benefit with mild hypothermia in these studies are the inclusion of patients with very severe traumatic injury, who are unlikely to benefit from any intervention, delay in achieving the target body temperature, and a possible deleterious effect of rewarming patients who were hypothermic at presentation.

The few studies of therapeutic hypothermia following stroke were primarily intended to assess feasibility and no large prospective randomised study has yet been reported.^{22–25}

In contrast to the predominantly negative studies of therapeutic hypothermia following traumatic brain injury and stroke, preliminary reports suggesting that mild hypothermia after cardiac arrest improved neurological outcome were substantiated by two randomised, controlled studies published in 2002. In these studies, 12–24 h of mild hypothermia resulted in an absolute risk reduction of 14–23% in adverse neurological outcome at 6 months.^{26 27}

STUDIES OF MILD HYPOTHERMIA IN NEWBORNS

Since accidental hypothermia in premature infants is harmful, the primary aim of preliminary clinical studies following perinatal asphyxia was to assess the safety of induced prolonged mild hypothermia.^{28–33} Cooling is associated with physiological changes in cardiovascular parameters: the blood pressure rises and heart rate

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Abbreviations: aEEG, amplitude integrated EEG; GMF, gross motor function; ICE, Infant Cooling Evaluation; MRC, Medical Research Council; NICHD, National Institute of Child Health and Human Development; PDI, psychomotor developmental index

falls linearly with cooling.^{29–34} The Q-T interval of the electrocardiogram increases with cooling, and arrhythmia has been observed in adults when the rectal temperature falls below 33°C,³⁵ although studies in infants suggest that there is little systemic effect in the treatment range (Edwards *et al*, unpublished data).

Hypothermia may also alter clotting and biochemical and metabolic measurements, but no clinically significant differences in blood viscosity, coagulation, or acidosis were noted between cooled and normothermic infants.^{29–32–36}

The first randomised controlled trial of therapeutic cooling after perinatal asphyxia has recently been reported in *The Lancet*.³⁹ Head cooling was achieved using a cap of coiled tubing filled with cooled fluid wrapped around the head. Excessive systemic cooling was prevented by the use of an overhead heater and shielding of the head. A total of 234 infants with moderate to severe encephalopathy and an abnormal aEEG were randomised to either head cooling for 72 h starting within 6 h of birth, with the rectal temperature maintained at 34.5°C, or to conventional care. After controlling for severity of encephalopathy determined by pre-randomisation aEEG, a protective effect of hypothermia was suggested ($p = 0.05$, odds ratio (OR): 0.57 (0.32, 1.01)). There was no effect of hypothermia in the 46 infants with the most severe aEEG abnormalities, but in the remaining 172 infants the combined outcome measure (death or severe disability) was reduced from 65.9% in controls to 47.6% in cooled infants ($p = 0.01$, OR 0.42 (0.22, 0.8)). In this less severe group, deaths were reduced from 38.6% to 28.6% and severe disability from 27.8% to 11.7%; however, these changes were not statistically significant. There were no clinically important complications associated with cooling. The inclusion of infants with very severe asphyxia may explain the lack of a neuroprotective effect of hypothermia in the total study population. In a subsidiary publication, the group presented a further analysis in which severity of encephalopathy judged by clinical assessment prior to randomisation was included in the equation and in this case the treatment was effective ($p < 0.05$).³⁷

A similarly sized study employing whole body cooling to 33.5°C for 72 h in infants selected by clinical assessment without EEG has also been completed very recently (the National Institute of Child Health and Human Development (NICHD) study).³⁸ Of 102 infants in the cooled group, 45 died or were disabled at 18 months compared with 64 of 106 control infants. The relative risk reduction was 0.72 (0.55–0.93) and 0.77 (0.6–0.98) after adjustment by centre and

severity of encephalopathy. Since this study which used only clinical selection criteria without aEEG and the head cooling study which included aEEG had similar adverse outcome rates in the control groups, currently, the role of aEEG for selecting infants in trials of neuroprotection is uncertain.

Some preliminary studies which were not powered to detect an effect on neurological outcome have also reported outcome.^{33–40} One such report found that in 65 asphyxiated newborns cooling reduced death or severe disability following asphyxia.³³ Other trials are in progress, including the Medical Research Council (MRC) funded TOBY trial in the UK which is recruiting ahead of target, the ICE (Infant Cooling Evaluation) trial in Australasia, and trials in Europe and China.

EVALUATING THE EVIDENCE

Combining the results of the CoolCap,³⁹ NICHD,³⁸ and Eicher³³ studies suggests that mild hypothermia is associated with a significant reduction in deaths and severe disability following asphyxia (fig 1). However, there are major differences between these studies which might invalidate such combined analysis. The three studies differed in the method of selection of infants, so the study groups may not be comparable as regards the methods and duration of cooling (which probably resulted in diverse brain temperatures in cooled infants) and as regards the assessment of outcome. In these three studies, the primary outcome measure was a combined outcome of death or disability, but the definition of disability varied between the studies. Whereas adverse outcome in the CoolCap study only included infants with severe disabilities (those with a Bayley's psychomotor developmental index (PDI) score of <70 or a gross motor function (GMF) score of 3–5 (non-ambulant, sitting with support)), the NICHD study included infants with less severe disabilities (a PDI of 70–85 or a GMF score of 2–5). Outcome was assessed at 18 months in the CoolCap and NICHD studies and at 12 months in the study by Eicher *et al*. We excluded the study reported by Battin *et al* from the speculative meta-analysis since it was an exploratory study of a combination of head cooling with varying degrees of systemic cooling, and group sizes were small.⁴⁰

Is hypothermia now a proven therapy which should become standard treatment in asphyxiated newborns? There are currently at least three ongoing large trials of hypothermia after asphyxia: the MRC funded TOBY trial,⁴¹ the neo.nEuro.network hypothermia trial in continental Europe,⁴² and the ICE trial in Australia. Should these trials

Review: Hypothermia
Comparison: Hypothermia versus normothermia
Outcome: Death or disability

Figure 1 Speculative meta-analysis of the effect of mild hypothermia on death or disability following perinatal asphyxia. The CoolCap study used selective head cooling with systemic cooling to 34.5°C for 72 h, and outcome assessed as death or severe disability at 18 months³⁴; the Eicher trial was a pilot study of whole body cooling to 33°C for 48 h with outcome assessed at 12 months³³; and the NICHD trial employed whole body cooling to 33.5°C for 72 h with assessment of death or moderate or severe disability at 18 months.³⁵

now stop enrolment and should hypothermic therapy be introduced universally into clinical practice?

To answer this question we need to ask if there are flaws in the presented trial data. If the data are robust, is the level of proof sufficient to remove equipoise for parents and professionals?

The quality of the trial data

Both the CoolCap and the NICHD studies were well constructed and executed trials with large professional organisations. CoolCap was industrially sponsored which raises a question mark in some observer's minds, but was carried out under rigorous protocols administered by the Federal Drugs Administration which maintain scientific standards in industrially sponsored research.

The result of CoolCap is positive and encouraging, particularly when further data given by the researchers is considered,³⁷ but there are some questions to consider concerning the analysis of the trial.

First, the trial was not blinded during treatment. This is inevitable given the nature of the treatment, but it may increase the possibility of unintentional and unquantifiable bias.

Second, the trial used a composite outcome measure: death or severe disability. This is unavoidable and appropriate, but composite outcome measures are often regarded by statisticians as increasing the precision of a trial at the cost of also adding to the uncertainty of the result.⁴³ This is not a problem as long as the trial is correctly interpreted, that is, that the result applies only to the composite outcome not to the components. In the current trial this means that we can make no statement concerning the effect of cooling on brain injury or the effect of cooling on death, but can only comment on the effect of cooling on adverse neurological outcome or death. This is clearly important, but it is not completely satisfactory to be unable to assess whether the treatment achieves the simple clinical goal of reducing brain damage.

Third, and perhaps most importantly, neurological outcome for the trial infants was assessed at 18 months. It is generally believed that it is not possible to completely exclude a diagnosis of cerebral palsy at this age, and certainly impossible to accurately define all cognitive defects. There have been examples in the past of early neurological assessments providing an over-optimistic assessment of the effect of treatments on neurological outcome; for instance, early assessment during the trial of different methods of cardiopulmonary bypass techniques carried out in Boston in the 1990s suggested that low flow bypass was superior to deep hypothermic cardiac arrest, but this was less evident at later examination.^{44, 45} Although it is unlikely that the 18 month assessment in the CoolCap trial has markedly underestimated severe cerebral palsy or death, later outcome assessments are needed to be confident that the beneficial effect of treatment is sustained, in particular that normal children do not develop disabling cognitive problems.

Finally, there is a statistical nicety in the analysis of the CoolCap study. The investigators stated in the trial design that they did not expect the treatment to be effective in the most severely asphyxiated infants, and quite properly defined a priori a subgroup analysis excluding these infants. However, many statisticians feel that subgroup analysis in general is a less robust approach than analysing the whole trial population for interactions which reveal the effect of severity. This analysis is not presented which some, although by no means all, observers feel may detract from the robustness of the analysis. The additional data presented go a considerable way to address this problem.³⁷

The NICHD trial shares the problems of blinding, composite outcome measure, and early neurological assessment. In

addition, many infants in the control group had elevated oesophageal temperature: the 75th centile was 37.5°C and in 41 infants it exceeded 38°C on at least one occasion. Since experimentally elevated body temperature is associated with a worse outcome following hypoxia ischaemia, it is plausible that the raised body temperature in the control group may have adversely influenced their outcome.

So what is the assessment of the quality of available data in these two large randomised trials? In general the trials were well executed. The numbers needed to treat in both trials are broadly similar, and neither showed any severe adverse effects. However, the residual concerns about methodology, assessment, and control arms should probably concern us, and not only because in both trials the levels of significance achieved by the data are perilously close to the time honoured 0.05 significance value. Small errors introduced by methodological concerns might abolish this technical level of significance.

Applying the data to patients

For a physician to offer a therapy to an individual, there must be no professional equipoise: the physician must believe the treatment is more likely to work than not. For a researcher to enrol a patient in a study, equipoise must exist and the researcher must believe that the benefit of the treatment is not known. The essential question for hypothermia is now therefore: is there equipoise about this treatment?

The question is one which considers individuals not study groups and is effectively, "do I believe that the person given this treatment will benefit from it or not?". A statistical formalism which addresses this issue is the bayesian approach of predictive probability, which in this case is the probability of success for the next patient treated. The approach calculates the probability density of the outcomes as a β density function, which with large numbers in a trial situation is likely to approximate a normal distribution when the predictive probability is the mean of this distribution and the 95% confidence limits for the prediction can be calculated.⁴⁶ 95% Confidence limits can be helpful in that if they cross the 0.5 probability it implies that treatment is unlikely to be successful.

This formalism gives us a useful way of considering the question of equipoise, as it focuses attention on the case of the individual considering a treatment. An example of a hypothetical case is given in fig 2. Here the β density function is calculated for a trial of 200 infants, of whom 100 were treated with drug x and 50 in each group had adverse outcome, in other words a completely fruitless trial with no evidence of either beneficial or noxious effect.

The β density curve has a mean probability of 0.5; this is the predictive probability and here is identical to the probability of a tossed coin being heads or tails. If the numbers in the trial increased but maintained the same proportion of good and bad outcome, the mean of the distribution and the predictive probability would remain 0.5 but the width of the distribution and the 95% confidence limits on that prediction would narrow. This point of 0.5 on the probability scale, the probability of a tossed coin being heads or tails, is the point of total uncertainty and is thus in one sense a point of equipoise.

This formalism can be applied to the available hypothermia trials. Under the important assumption that the trial data are absolutely robust and genuinely reflect the real effect of the treatment, the β density function for the CoolCap trial is presented in fig 3. The predictive probability is 0.56 (95% CI 0.49 to 0.62), implying that the next appropriately recruited child treated by the CoolCap method has a 56% chance of good outcome. The CoolCap study shows best effect if infants with the most severe presentations are excluded; if the

patient is not in this group the probability that CoolCap treatment will be beneficial is 0.59 (95% CI 0.52 to 0.67).

EQUIPOISE

The bayesian plots underline the point that although the results of the trials are significant at $p < 0.05$, this does not mean that an individual child has a 95% chance of benefiting from cooling; indeed, for an individual the chance of good outcome if treated may improve by only a few percentage points.

Is this chance good enough to remove our equipoise and mandate that this child should receive the therapy? This is not a simple question. Equipoise is not a single point which is the same for everyone. Different people judge evidence differently and take different views of equipoise; indeed, some commentators have argued for the concept of communal equipoise, where a community is regarded as being in equipoise until all the individuals in it have lost their personal uncertainty.⁴⁷

This may be slightly unwieldy for a practical application, but it emphasises the essential truth that equipoise is an individual decision faced by a particular individual with a particular prediction of the outcome of treatment. A parent faced with an asphyxiated child may ask, "will the treatment do any harm?" and if the answer is "probably not", decide that even the slightest hint of benefit is enough to make them want the treatment for their child, so that equipoise could be lost even without conventional statistical proof. On the other hand, a well-informed physician charged with making a professional assessment of the data for the family may correctly demand a different standard of proof before advising treatment. The professional has to consider many issues such as the opportunity cost of a therapy, particularly when establishing the protocols for treating patients in general.

Indeed, not only do individuals have differing equipoise, but a single person may lose equipoise differently depending on their social role. Our hypothetical physician may assess the data as insufficiently robust for her to advise a national programme of treatment without further research, but with complete logical consistency wish that her own asphyxiated child be treated. Equipoise is thus not a single definable value in a probability analysis, and the value of 0.5 (the point of total uncertainty) on figs 2 and 3 may not be an adequate description of equipoise, indeed perhaps a broader fuzzy line might be more appropriate.

Figure 2 Predictive probability for a hypothetical ineffective treatment. The graph shows the probability distribution (modelled as a β density) created by a hypothetical trial of 200 patients in which the numbers of successful outcomes were equal in both treatment and control groups. The mean of the distribution is 0.5 (shown by a dotted line), showing that the chance of treatment being successful is exactly 50%, or equivalent to a tossed coin being heads or tails.

Figure 3 Predictive probability that head cooling improves outcome for infants with moderately severe neonatal encephalopathy as predicted by the CoolCap study. The chance that cooling will benefit the next patient treated is the mean of the distribution (0.59) and the lower 95% confidence limit is 0.52.

What could we do about this? The answer is to increase the precision of the estimate, in other words to reduce the width of the β density curve. An attraction of the bayesian approach is that more data can be added to a dataset to make new estimates without violating any statistical assumptions. More studies of hypothermia will thus allow us to increase the precision of our estimate and gain confidence in our prediction of the benefit to each child we treat. Obviously, because we regard the available trial data as fundamentally of high quality even with the caveats given above, we would not expect that the point estimate of predictive probability will change very much, only that we become more confident of it.

The central question is whether hypothermic neural rescue therapy should now be used outside randomised controlled trials. Our view is that the data currently are suggestive and encouraging, but not sufficiently strong to mandate treatment outside trials. We would encourage the use of hypothermia within research protocols, and we are hopeful that soon the data will be precise enough to support a change in health policy. This view is entirely in agreement with the statement of an expert group recently formed by the National Institute of Health in the United States and soon to be made public.

CONCLUSIONS

The trials of hypothermic neural rescue therapy for infants with neonatal encephalopathy that have recently been reported are well constructed and analysed. The data suggest that either selective head cooling or total body cooling reduces the combined chance of death or disability after birth asphyxia. However, there are still unanswered questions about the treatments which mean that many professionals may still feel that further data are needed before health care policy changes can be made to make cooling the standard of care for all babies with suspected birth asphyxia.

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